REMARKS

Reconsideration of the rejection of all claims is respectfully requested in view of the above amendments and the following remarks.

AMENDMENTS

Specification Amendments

Reference to the PCT application, of which the present application is the US National Stage, has been inserted before the first paragraph of the specification, as requested by the Examiner.

Claim Amendments

Claims 2-3, 10-12 and 15-21 have been cancelled, leaving claims 1, 4-9 and 13-14 pending in this application after entry of the above amendments. The remaining claims have been amended as follows:

All claims have been amended, either directly or through dependency on an amended claim, to more specifically define the "prodrug" as "an *in vivo* hydrolysable ester formed on an available carboxy or hydroxy thereof, or an *in vivo* hydrolysable amide formed on an available carboxy thereof." Support is found in the specification as filed, *e.g.*, at page 3, line 29 through page 4, line 22. Support for this amendment will be discussed further below in relation to the enablement rejection with respect to the term "prodrug."

Claim 1 has been further amended to incorporate the limitations of original claim 2, whereby R^1 and R^2 are both butyl.

Claim 2 has been cancelled as now being duplicative of claim 1.

Claim 3 has been cancelled for consistency with amended claim 1.

Claims 4-6, 8-9 and 13-14 have been further amended with respect to their dependency, to update their dependency in view of claim cancellation, to appropriately recite dependency and/or to avoid improper multiple dependencies.

Claims 8-10 have been further amended to delete the phrase "as depicted above," which the Examiner found indefinite in the rejection of paragraph 5.b) at page 6 of the Action.

Claim 8 has been further amended to delete the compound "1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxy-3-methylsulphonylpropyl)-carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine," which, as the Examiner has pointed out in the rejection of paragraph 5.a) (Action page 6), is a duplicate of the next compound in the list of claim 8, "1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxy-3-mesylpropyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine."

Claim 9 has been further amended to change the subjective phrase "if necessary or desirable" to the more objective phrase "optionally" with respect to the optional further process steps recited at the end of this claim.

The format of **original method claim 13** as been changed from "a method for producing an IBAT inhibitory effect" to "a method for inhibiting IBAT," which is believed to be more in accord with the format currently favored by Group 1600. Support and enablement for the presently claimed compounds inhibiting IBAT is found in the specification, *e.g.*, at page 2, lines 19-20 and in the *in vitro* and *in vivo* test assays discussed at page 16, lines 22-27.

Claim 13 has been further amended to delete the term "such as man" as not further limiting the claim and generally being considered inappropriate under US practice.

Claims 13 and 14 have been further amended to refer to compounds of formula **(I')** as well as compounds of formula **(I)**, inasmuch as these claims are also dependent on claim 7, which is directed toward compounds of formula **(I')**.

The above amendments are made without abandonment or prejudice to Applicants' right to prosecute any subject matter thereby removed from the scope of the present claims in one or more continuing applications.

RESPONSE TO DETAILED ACTION

In response to the Detailed Action portion of the current Action commencing at page 2, Applicants respond as follows, maintaining the Examiner's sequence of rejections and comments as set forth in the Action.

Priority

As suggested by the Examiner in paragraph 1 (at page 2) of the Action, reference to the PCT application of which the present application is the US National Stage has been inserted before the first paragraph of the specification.

Claim Rejections - 35 USC § 112, 1st Paragraph

Enablement of "Prodrug"

Claims 1-21 have been rejected in paragraph 2 (at pages 2-3) of the Action under 35 U.S.C. § 112, first paragraph, on grounds that the claim term "prodrug" is not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the Examiner asserts:

> The nature of the invention in the instant case, has claims which embrace 1,1-dioxo-2,3,4,5-tetrahydro-1,5-benzothiazepine compounds. The scope of "prodrug" is not adequately enabled. Applicants provide no guidance as how the compounds are made more active in vivo. The choice of a "prodrug" will vary from drug to drug. Therefore, more than minimal routine experimentation would be required to determine which prodrug will be suitable for the instant invention.
>
> The instant compounds of formula (I) wherein the prodrugs are not described in the disclosure in such a way the one of ordinary skill in the art would no how to prepare the various compounds suggested by claims 1-16 and 20-76 [sic]. In view of the lack of direction provided in the specification regarding starting materials, the lack of working examples, and the general unpredictability of chemical reactions, it would take an undue amount of experimentation for one skilled in the art to make the claimed compounds and therefore practice the invention.

(Action at page 3).

Applicants maintain that the specification is enabling for the term "prodrug" as it is used in the context this specification and claims, when one considers the extensive knowledge and experience with prodrugs of this nature in the pharmaceutical arts, and in particular in view of the guidance provided in the specification at, *e.g.*, pages 3-4. Nevertheless, in order to expedite prosecution of this application to an early allowance, the claims have been amended above to more specifically define the prodrugs as "an *in vivo* hydrolysable ester formed on an available carboxy or hydroxy thereof, or an *in vivo* hydrolysable amide formed on an available carboxy thereof."

The nature of the esters within the scope of the claims, formed on an available carboxy or hydroxy group of a compound of formula **(I),** is described beginning at page 4, line 1. Specific examples of pharmaceutically acceptable esters that can be formed on carboxy groups are recited at page 4, lines 1-9. Specific examples of pharmaceutically acceptable esters that can be formed on hydroxy groups are recited at page 4, lines 10-19. Specific examples of hydrolysable amides that can be formed on carboxy groups are recited at page 4, lines 20-22.

Moreover, the level of skill and knowledge of persons skilled in this art with respect to the formation and structure of prodrugs is very high, particularly including *in vivo* hydrolysable esters and/or amides, as evidenced by the hundreds of patents issued before the priority date of the present application having claims including such prodrugs, esters and/or amides. These references make clear that persons skilled in the art will have no difficulty in understanding and practicing the preparation and use of prodrugs including *in vivo* hydrolysable or cleavable esters or amides. Some of these references refer the reader to literature references for more details if needed. Excerpts from a few of these many patents are as follows:

U.S. Patent 5,866,568 (Issued February 2, 1999)

> It will further be appreciated that a compound of the formula I may be chemically modified such that in vivo it is converted into a parent compound of the formula I (for example, by hydrolytic, oxidative or enzymatic cleavage). Such chemically modified compounds are commonly referred to as prodrugs and may be, for example, metabolically labile ester or amide derivatives of a parent compound

having a carboxylic acid group (or a metabolically labile ester of a parent compound having a hydroxy group). It is to be understood that the present invention also concerns any such prodrugs, including metabolically labile ester or amide derivatives of compounds of the formula I. (Col. 3, line 63 to col. 4, line 6).

* * * * *

Examples of metabolically labile ester derivatives of a carboxy group are esters formed with alcohols such as (1-6C)alkanols, for example methanol, ethanol, propanol and isopropanol; indanol; adamantol; (1-6C)alkanoyloxy(1-4C)alkanols such as pivaloyloxymethyl; glycolamides; (S-methyl-2-oxo-1,3-dioxol-4-yl)methyl alcohol; and (1-4C)alkyloxycarbonyl(1-4)alkanols.

Examples of metabolically labile amide derivatives of a carboxy group include amides formed from ammonia and amines such as (1-4C)alkylamine, for example methylamine, di(1-4C)alkyl amines, (1-4C)alkoxy(1-4C)alkylamines such as methoxyethyl amine, phenyl(1-2C)alkylamines such as benzylamine; and amino acids such as glycine or an ester thereof.

It will be appreciated that where sub-groups of compounds of the invention, or particular or preferred groups of compounds of the invention or specific compounds of the invention are referred to, these groups include prodrugs of said compounds, such as metabolically labile esters or amides. (Col. 11, lines 22-41).

* * * * *

Additionally, a compound of the formula I may be converted into a prodrug (for example, a metabolically labile ester or amide) by methods well known in the art. For example, a pharmaceutically acceptable metabolically labile ester or amide may be formed respectively by estcrifying a compound of the formula I bearing a carboxylic acid (or hydroxy) group or reacting the carboxylic acid group (or a reactive derivative thereof) with the appropriate amine, using conventional techniques. (Col. 14, lines 35-43).

U.S. Patent 5,726,182 (issued March 10, 1998)

The term "prodrug", as of the compounds of formula I, refers to derivative compounds that are rapidly transformed in vivo to yield the parent compound of the formula I, as for example by hydrolysis in blood. T. Higuchi and V. Stella provide a thorough discussion of the prodrug concept in "Pro-drugs as Novel Delivery Systems", Vol 14 of the A.C.S. Symposium Series, American Chemical Society (1975).

Examples of esters useful as prodrugs for compounds containing carboxyl groups can be found on pages 14-21 of "Bioreversible Carriers in Drug Design: Theory and Application", edited by E. B. Roche, Pergamon Press: New York (1987). It is intended that these references, and any others cited throughout this specification, are incorporated herein by reference.

The term "prodrug ester group" refers to any of several ester-forming groups that are hydrolyzed under physiological conditions. Examples of prodrug ester groups include pivoyloxymethyl, acetoxymethyl, phthalidyl, indanyl and methoxymethyl, as well as other such groups known in the art, including a (5-R-2-oxo-1,3-dioxolen-4-yl)methyl group. Other examples of prodrug ester groups can be found in the book "Pro-drugs as Novel Delivery Systems", by Higuchi and Stella, cited above. (Col. 21, lines 10-31).

U.S. Patent 5,616,591 (issued April 1, 1997)

It should be understood that the present invention includes prodrug forms, such as ester, acetal and/or mixed acetal derivatives of the compounds of formula I. For example, such derivatives have been documented in Design of Prodrugs, edited by H. Bundgard, (Elsevier, 1985) and Methods in Enzymology, Vol. 42, p. 309-396, edited by K. Widder et al. (Academic Press, 1985). Further, it is understood that any moiety at R_6 and/or R_7 that will be cleaved in vivo to provide an acidic R_6 and/or R_7 moiety is within the spirit and scope of this invention. (Col. 3, lines 57-67).

U.S. Patent 5,468,757 (issued November 21, 1995)

Prodrugs are derivatives of the compounds of the invention which have chemically or metabolically clearable groups and become by solvolysis or under physiological conditions the compounds of the invention which are pharmaceutically active in vivo. Derivatives of the compounds of this invention have activity in both their acid and base derivative forms, but the acid derivative form often offers advantages of solubility, tissue compatibility, or delayed release in a mammalian organism (see, Bundgard, H., Design of Prodrugs, pp. 7-9, 21-24, Elsevier, Amsterdam 1985). Prodrugs include acid derivatives well known to practitioners of the art, such as, for example, esters prepared by reaction of the parent acidic compound with a suitable alcohol, or amides prepared by reaction of the parent acid compound with a suitable amine. Simple aliphatic or aromatic esters derived from acidic groups pendent on the compounds of this invention are preferred prodrugs. In some cases it is desirable to prepare double ester type

> prodrugs such as (acyloxy) alkyl esters or ((alkoxycarbonyl)oxy)alkyl esters. (Col. 7, line 62 through col. 8, line 14).

Thus, in addition to the disclosure in the present specification at pages 3-4, the pharmaceutical art is replete with guidance (both in literature and issued patents) on making prodrugs of pharmaceutical compounds, including in ester or amide form which would be "*in vivo* hydrolysable." It is respectfully submitted that the skilled person, drawing on the wealth of information and knowledge already available in the art, and the guidance and specific examples provided in the specification, would have no difficulty in making or using the invention as now claimed without the need for "undue experimentation."

As a point of clarification, the Examiner asserts at page 3 of the Action that "**more than minimal routine experimentation** would be required" to determine which prodrug will be suitable for the instant invention (emphasis added). It is respectfully submitted that the case law test of "**undue experimentation**" permits significantly more experimentation than "minimal routine experimentation" while still meeting the enablement requirements. Thus, the Federal Circuit has repeatedly made clear that the emphasis is on "undue", not whether more than minimal experimentation may be required. See, for example, *PPG Industries Inc. v. Guardian Industries Corp.* 37 USPQ2d 1618, 1623 (Fed. Cir. 1996):

> Enablement is lacking in those cases, the court has explained, because the undescribed embodiments cannot be made, based on the disclosure in the specification, without undue experimentation. But the question of undue experimentation is a matter of degree. The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation "must not be unduly extensive." *Atlas Powder Co. v. E.I. DuPont De Nemours & Co.*, 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984). The Patent and Trademark Office Board of Appeals summarized the point well when it stated:
>
> > The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed.

Ex parte Jackson, 217 USPQ 804, 807 (1982).

It is respectfully submitted that, in view of the extensive knowledge in the art at the time of the present invention pertaining to prodrugs in general and *in-vivo* hydrolysable esters and amides in particular, and the guidance provided by the present specification, any experimentation that might have been required to practice this embodiment of the present invention would have been, at worst, a routine matter and certainly not "undue" as that term is used by the Federal Circuit. Withdrawal of this ground for rejection is therefore believed to be in order and is respectfully requested.

Enablement of Method Claims

Claims 10-21 have been rejected in paragraph 3 (at pages 3-5) of the Action under 35 U.S.C. § 112, first paragraph, on grounds that these claims are not enabled by the specification. However, **in this paragraph 3** of the Action the Examiner only specifically applies this rejection to method claims 12 and 13 (which are characterized as being directed toward "a method of treating a disease, which is associated with the inhibition of IBAT), asserting that the specification enablement is not commensurate with the scope of the claimed methods for treating a disease associated with the inhibition of IBAT.[1] Specifically, the Examiner asserts:

> HOW TO USE: Claims 12 and 13 are to a method of treating a disease, which is associated with the inhibition of IBAT. Any evidence presented must be commensurate in scope with the claims and must clearly demonstrate the effectiveness of the claimed compounds. The scope of the method claims are not adequately enabled solely based on inhibition of IBAT provided in the specification. Diseases and/or disorder(s) known to be associated with ileal bile acid transport (IBAT) inhibitory activity include atherosclerosis. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. It is difficult to treat many of the disorders claimed herein.

[1] It is noted that the remainder of the claims generally recited at the beginning of this paragraph 3 rejection are **composition** claims, not method claims, and all of these remaining composition claims (**except for claim 14**) are specifically rejected in **paragraph 4** (at page 5) of the Action for lack of enablement of the **complex** compositions (multiple active components) recited in these claims. This discussion of the paragraph 3 rejection will therefore be limited to the method claims, and the paragraph 4 rejection will be discussed in the next section of this Response.

> No screening protocol(s) are ever described. Thus, no evidence of in vitro effectiveness is seen in the specification for one of the instantly claimed 1,1-dioxo-2,3,4,5-tetrahydro-1,5-benzothiazepine compounds. In general, pharmacological activity is a very unpredictable area. In cases involving physiological activity "the scope of the enablement obviously varies inversely with the degree of unpredictability of the factors involved." In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970). Since this case involves unpredictable in-vivo physiological activities, the scope of the enablement given in the disclosure presented here was found to be low.
>
> The specification has no working examples on the use of the substituted 1,1-dioxo-2,3,4,5-tetrahydro-1,5-benzothiazepine, etc. There must be evidence to justify the contention that the claimed compounds can be useful in the treatment of atherosclerosis, arteriosclerosis, arrhythmia, hyper-thrombotic conditions, vascular dysfunction, endothelial dysfunction, heart failure, coronary heart diseases, cardiovascular diseases, myocardial infarction, angina pectoris, peripheral vascular diseases, inflammation of cardiovascular tissues, aneurisms, stenosis, restenosis, vascular plaques, vascular fatty streaks, leukocyte, monocytes and/or macrophage infiltrate, intimital thickening, medial thinning, infectious and surgical trauma and vascular thrombosis, stroke, transient ischaemic attacks, etc.

(Action at pages 4-5).

In order to expedite the prosecution of this application to allowance, and without agreeing or implying any agreement with this ground for rejection, this rejection with respect to method claim 12 has been obviated by the cancellation of such claim. However, this ground for rejection with respect to remaining method claim 13 is respectfully traversed.

Claim 13 differs from the Examiner's assertions in that it recites the direct action of the presently claimed compounds in inhibiting IBAT in a warm-blooded animal, rather than the treatment of one or more specific disease or medical condition. Inasmuch as the clear focus of this rejection is on enablement of the specific disease conditions, it is believed that this ground for rejection is inapplicable to claim 13. Moreover, the Examiner's attention is drawn to the specific disclosure at page 16, lines 22-27 of the specification with respect to test assays to determine the IBAT inhibitory activity of the claimed compounds. It is therefore submitted that the specification, when considered with knowledge already present in the art, clearly enables one to inhibit IBAT in a warm-blooded animal as claimed in claim 13, and this ground for rejection of claim 13 should be withdrawn.

Enablement of "Complex Composition" Claims

Claim 15-21 have been rejected in paragraph 4 (at page 5) of the Action under 35 U.S.C. 112, first paragraph, on grounds that these claims are not enabled by the specification with respect to the "complex compositions" (*i.e.*, including an additional active component) recited in these claims. Specifically, the Examiner asserts:

> Claims 15-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the pharmaceutical compositions of the compounds of formula I, does not reasonably provide enablement for the complex compositions of formula I as claimed herein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The pharmaceutical compositions and method of use of the instant invention where an additional active ingredient such as **HMG Co-A reductase inhibitors, bile acid binder, PPAR alpha and/or gamma agonist** is included in the compositions. The specification does not define that which is intended in the additional active ingredients, i.e. which HMG Co-A reductase inhibitors, bile acid binder, PPAR alpha and/or gamma agonist, etc.

(Action at page 5; emphasis in original).

For clarity, it should be noted that claims 15-21 rejected in this paragraph 4 recite complex compositions *per se* wherein an additional active component is present. In order to expedite the prosecution of this application to allowance, and without agreeing or implying any agreement with this ground for rejection, this rejection with respect to all of claims 15-21 has been obviated by the cancellation of each such claim.

It should again be noted that although **pharmaceutical composition claim 14** was included within the claims generally recited at the beginning of the paragraph 3 rejection (Action page 3), this pharmaceutical composition claim was **not** specifically recited in the rejection of **method of treatment** claims in the paragraph 3 rejection nor in the rejection of **complex composition** claims in the paragraph 4 rejection. This is appropriate inasmuch as pharmaceutical composition claim 14 is directed toward a "pharmaceutical composition which comprises a compound of formula **(I)** or formula **(I')** . . . as claimed in any one of claims 1 and 4 to 11, in association with a pharmaceutically-acceptable diluent or carrier," and is **neither a method** of treatment claim **nor a complex** composition claim including an

additional active component. Thus it is presumed that the inclusion of claim 18 in the general recitation of rejected claims in the introductory portion of the paragraph 3 rejection was inadvertent, and that the only lack of enablement rejection of claim 18 was with respect to the term "prodrug" in the paragraph 2 rejection, which it is believed has been overcome by the amendment to that term as discussed above.

Claim Rejections - 35 USC § 112, 2nd Paragraph

Claims 8-13 are rejected (paragraph 5 at pages 6-9) of the Action under 35 U.S.C. 112, second paragraph, as being indefinite for the reasons itemized in subparagraphs a) through f). Claims 10-12 have been cancelled, as noted above, thereby obviating this rejection with respect to those claims. This ground for rejection as applicable to claims 8-9 and 13-14 will be addressed below with reference to each lettered subparagraph of this rejection as quoted below.

a) Claim 8 is vague and indefinite in that it is not known what is meant by the second occurrence of the species 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxy-3 mesylpropyl)carbamoyl]benzyl}-carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine in lines 24-25 on page 40, which is a duplicate of 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*M*-((*S*)-1-carboxy-3-methylsulphonylpropyl)carbamoyl]-benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine in lines 21-23.

This ground for rejection has been overcome by the amendment to claim 8 removing reference to "1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxy-3-methylsulphonylpropyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine."

b) Claim 9 is vague and indefinite in that it is not known what is meant by "a compound of formula (I)" which is not present in independent claim 9.

This ground fur rejection has been overcome by the amendment to claim 9, inserting "as claimed in claim 1."

c) Claims 10-12 are a substantial duplicate of claim 14 as the only difference is a statement of intended use, which is not given material weight. Note In re Tuominen 213 USPQ 89.

This ground for rejection has been obviated by the cancellation of the involved claims as being in a "use" format not generally accepted under US practice.

d) **Claim 12 provides for the use of the compounds of formula (I), but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.**

This ground for rejection has been obviated by the cancellation of the involved claims as being in a "use" format not generally accepted under US practice.

e) **Claims 12 and 13 are vague and indefinite in that the claim provides for the use of claimed compounds, but the claim does not set forth any steps involved in determining which are the disorders capable of being treated by modulating the activity of ileal bile acid transport (IBAT). Determining whether a given disease responds or does not respond to such an inhibitor will involve undue experimentation. Suppose that a given drug, which has inhibitor properties in vitro, when administered to a patient with a certain disease, does not produce a favorable response. One cannot conclude that specific disease does not fall within this claim.**

In this subparagraph, claims 12 and 13[2] have been rejected under 35 U.S.C. § 112, **second** paragraph, as being "vague and indefinite in that the claim provides for the use of claimed compounds, but the claim does not set forth any steps involved in determining which are the disorders capable of being treated by modulating the activity of ileal bile acid transport (IBAT)." The Examiner then asserts that "determining whether a given disease responds or does not respond to such an inhibitor **will involve undue experimentation**" (Action at page 7; emphasis added). It is respectfully submitted that the Examiner has not made out an appropriate rejection under section 112, **second** paragraph, and that this rejection is at best a duplicate of the section 112, **first** paragraph rejection set out in paragraph 3 of the Action, beginning with the first full paragraph on page 4 of the Action, which was addressed and overcome at pages 21-23 above.

[2] This ground for rejection with respect to claim 12 has been obviated by the cancellation of such claims as being in a "use" format not generally accepted under US practice.

In this regard, the Examiner's attention is called to **MPEP ¶ 2174** [3], which is reproduced in full below for the Examiner's convenience:

> **2174 Relationship Between the Requirements of the First and Second Paragraphs of 35 U.S.C. 112**
>
> The requirements of the first and second paragraphs of 35 U.S.C. 112 are separate and distinct. If a description or the enabling disclosure of a specification is not commen-surate in scope with the subject matter encompassed by a claim, that fact alone does not render the claim imprecise or indefinite or otherwise not in compliance with 35 U.S.C. 112, second paragraph; rather, the claim is based on an insufficient disclosure (35 U.S.C. 112, first paragraph) and should be rejected on that ground. I*n re Borkowski*, 422 F.2d 904, 164 USPQ 642 (CCPA 1970). If the specification discloses that a particular feature or element is critical or essential to the practice of the invention, failure to recite or include that particular feature or element in the claims may provide a basis for a rejection based on the ground that those claims are not supported by an enabling disclosure. *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976). In *Mayhew*, the examiner argued that the only mode of operation of the process disclosed in the specification involved the use of a cooling zone at a particular location in the processing cycle. The claims were rejected because they failed to specify either a cooling step or the location of the step in the process. The court was convinced that the cooling bath and its location were essential, and held that claims which failed to recite the use of a cooling zone, specifically located, were not supported by an enabling disclosure (35 U.S.C. 112, first paragraph).
>
> In addition, if a claim is amended to include an invention that is not described in the application as filed, a rejection of that claim under 35 U.S.C. 112, first paragraph, as being directed to subject matter that is not described in the specification as filed may be appropriate. *In re Simon*, 302 F.2d 737, 133 USPQ 524 (CCPA 1962). In *Simon*, which involved a reissue application containing claims to a reaction product of a composition, applicant presented claims to a reaction product of a composition comprising the subcombination A+B+C, whereas the original claims and description of the invention

[3] Eighth Edition, Rev. 4, October 2005 (available on US PTO Website; this paragraph is identical to ¶2174 reproduced at page 2100-228 of the printed MPEP of Rev. 3, August 2005).

> were directed to a composition comprising the combination A+B+C+D+E. The court found no significant support for the argument that ingredients D+E were not essential to the claimed reaction product and concluded that claims directed to the reaction product of a subcombination A+B+C were not described (35 U.S.C. 112, first paragraph) in the application as filed. See also *In re Panagrossi,* 277 F.2d 181, 125 USPQ 410 (CCPA 1960).

(MPEP ¶ 2174; emphasis added).

It is therefore submitted that the Examiner has inappropriately recharacterized the previous section 112, **first** paragraph non-enablement rejection of these same claims as a **second** paragraph indefiniteness rejection, even to the point of applying the **first** paragraph "undue experimentation" test to this purported **second** paragraph rejection. If the Examiner is attempting to raise some other aspect of *non-enablement* of these claims not raised elsewhere in the Action, Applicants will respond if a proper rejection is made under section 112, **first** paragraph.

In any event, as explained in response to the section 112, **first** paragraph, rejection above (and for the reasons and qualifications there stated), *any* rejection with respect to method claim 12 has been obviated by the cancellation of such claim. It was also pointed out that claim 13 differs from the assertions made by the Examiner in that it recites the direct action of the presently claimed compounds in inhibiting IBAT in a warm-blooded animal, rather than the treatment of one or more specific disease or medical condition. Inasmuch as the clear focus of this rejection as well is on enablement of the specific disease conditions, it is believed that this ground for rejection (however characterized) has been overcome. In this regard, the Examiner's attention is also drawn to the specific disclosure at page 16, lines 22-27 of the specification with respect to test assays to determine the IBAT inhibitory activity of the claimed compounds. Therefore, it is respectfully submitted that *even if* this ground for rejection (to the extent understood) were properly characterized as a non-enablement rejection under section 112, **first** paragraph, any such rejection has been obviated or overcome.

f) Regarding claim 13, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

This ground for rejection has been overcome with respect to claim 13 by the above amendment that removes the phrase "such as man" from claim 13.

Claim Rejections - 35 USC § 101

This ground for rejection has been obviated by the cancellation of claim 12.

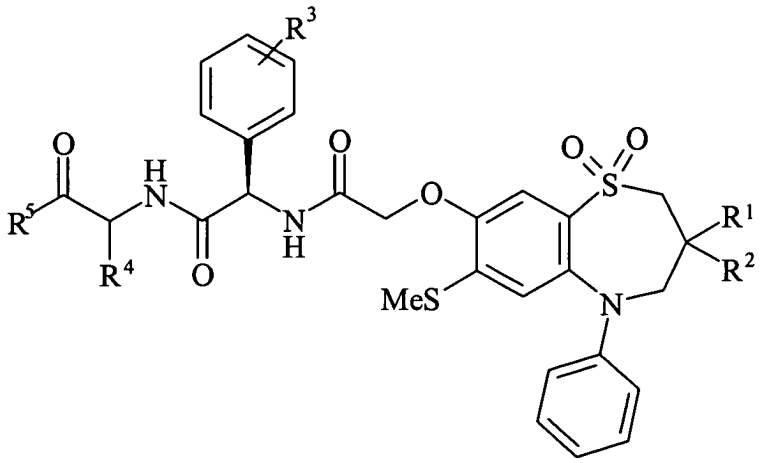
Double Patenting

Various of the claims have been rejected for obviousness-type double patenting over multiple references. Applicants disagree that obviousness-type double patenting could arise from the invention described in at least most of these references relative to the invention of the present application. However, this issue need not be addressed at this time with respect to the cited co-pending applications inasmuch as the rejection remains provisional (no claims allowed or issued in the co-pending application), and/or the issue has been rendered moot because of the cancellation of the affected claims, for reasons noted above and unrelated to these obviousness-type double patenting rejections. Each of the references will be separately addressed below in the order raised by the Examiner.

US Patent 6,906,058

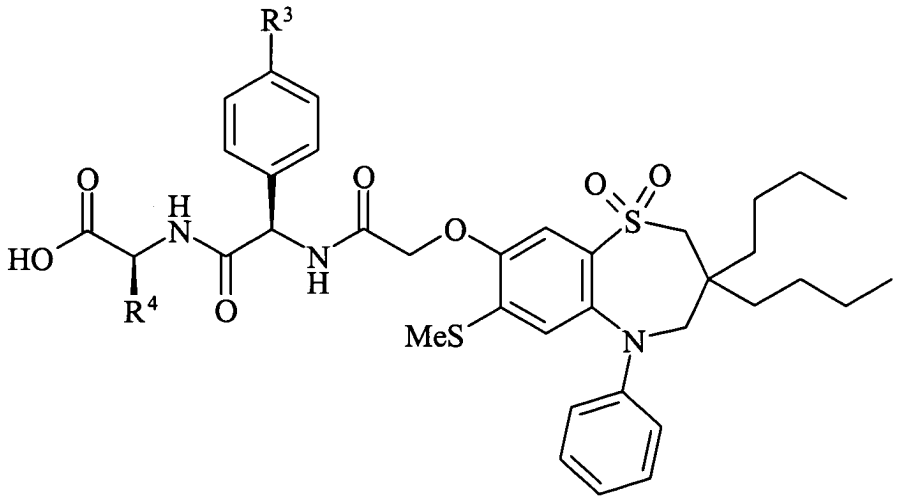
Claims 1-14 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8 and 11 of U.S. Patent No. 6,906,058 (hereinafter "the '058 Patent"). The Examiner asserts that "although the conflicting claims are not identical, they are not patentably distinct from each other because the compounds, compositions, process of preparing and method of use of the compounds of formula (I) embrace the compounds, compositions and method of use of the compounds of formula (I) of U.S. '058 where D is O." (Action paragraph 7 at page 10; emphasis added). This ground for rejection is respectfully traversed on the ground, *inter alia*, that the claims of the present application do not embrace any compound, composition, or method of use of the compounds of formula (I) claimed in the '058 Patent, whether or not D is O.

The present claims are directed toward compounds, compositions, methods and processes for making compounds of formula **(I)** (claim 1 and claims dependent thereon):



(I)

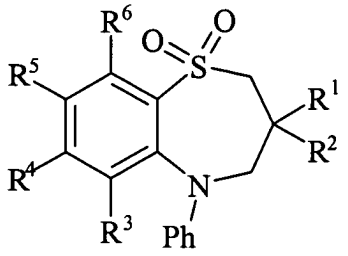
or a compound of group of formula **(I')** (claim 7 and claims dependent thereon):



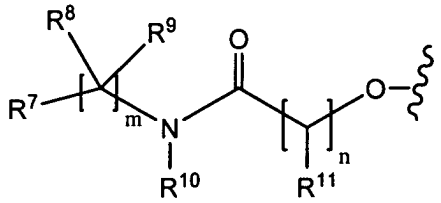
(I')

In both formulae, the 8-position substituent on the benzothiazepine has a <u>phenyl ring directly bound</u> to the carbon adjacent to the nitrogen of the -N(H)C(O)CO- group of that substituent. This phenyl is, of course, <u>totally unsaturated</u>. No compound claimed in the '058 Patent has such a totally unsaturated ring, no less a phenyl ring, in the position of that phenyl ring on the 8-position benzothiazepine substituent of the present claims.

Specifically, the '058 Patent claims compounds of formula **(I)**:



wherein one of R^4 and R^5 is a group of formula (IA):



The carbon adjacent -N(R^{10})C(O)- in this formula (IA) bearing groups R^7, R^8 and R^9 corresponds to the carbon to which the phenyl ring is directly bound in the compounds of the present claims. However, none of R^7, R^8 and R^9, individually or in combination as defined in the '058 Patent, can provide a totally unsaturated ring (no less a phenyl ring) directly bound to the formula (IA) chain carbon, as required in the present claims.

In generic claim 1 of the '058 Patent, R^8 and R^9 may independently be "a saturated cyclic group." The term "saturated cyclic group" is defined in the '058 Patent at column 4 as follows:

> A "saturated cyclic group" is a totally or partially saturated, mono or bicyclic ring containing 3-12 atoms of which 0-4 atoms are chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked. Preferably "saturated cyclic group" refers to a totally saturated, monocyclic ring containing 5 or 6 atoms or a totally saturated bicyclic ring containing 9 or 10 atoms of which 0-4 atoms are chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked. Examples and suitable values of the term "saturated cyclic group" are cyclohexyl, cyclopropyl, pyrrolidinyl, morpholino and piperidyl. Preferably "saturated cyclic group" is cyclohexyl.

('058 Patent at col. 4, lines 14-26; emphasis added). Thus, the definition of R^8 and R^9 in the '058 Patent very specifically does not encompass a totally unsaturated ring, no less a phenyl

ring, and, in fact, teaches against even a partially saturated ring by its clear preference for a totally saturated ring, most preferably cyclohexyl, .

In working through the more remote combinations of moieties as defined in generic claim 1 of the '058 Patent, it is noted that R^8 and R^9 may independently be C_{1-4}alkyl (col. 58, line 60), and that R^8 and R^9 may be independently optionally substituted on carbon by one or more substituents selected from R^{15} (col. 58, lines 62-64). The definition of R^{15} at col. 59, lines 39-55 includes, among numerous other selections, carbocyclyl and heterocyclyl. A "heterocyclyl" is defined at column 4, lines 27-30, as "a saturated, partially saturated or unsaturated, mono or bicyclic ring containing 3-12 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen," and a "carbocyclyl" is defined at column 4, lines 56-58, as "a saturated, partially saturated or unsaturated, mono or bicyclic carbon ring that contains 3-12 atoms." Thus, by a combination of selections of various substituents it is possible to have an unsaturated ring, such as a phenyl ring, indirectly attached to that formula (IA) chain carbon, *e.g.*, via a methylene group, but there is no structure within even the broadest genus of claim 1 of the '058 Patent that meet the requirements of the phenyl ring on the 8-position substituent in formula **(I)** or formula **(I')** of the present claims, wherein a totally unsaturated phenyl ring must be directly bound to the carbon adjacent the nitrogen of the -N(H)C(O)CO- group of that 8-position substituent.

Thus, there is no overlap between the compounds recited in the present claims and even broadest generic claim definition of the '058 Patent claims. Therefore the Examiner's assertion upon which this rejection is based, that the compounds of the present claims embrace compounds of formula (I) of the '058 Patent, is clearly in error, and this ground for rejection should be withdrawn.

Moreover, there is no suggestion in the '058 Patent that might motivate the skilled person to substitute a phenyl ring in the '058 Patent structure at the equivalent location of the phenyl ring on the 8-position substituent of the present claims. In fact, the '058 Patent expressly teaches to the contrary. As noted above, claim 1 of the '058 Patent provides that R^8 and R^9 can independently be "hydrogen, C_{1-4}alkyl or a saturated cyclic group," and further provides that when R^8 or R^9 is a C_{1-4}alkyl, it may optionally be substituted with an R^{15} group, which includes "carbocyclyl" or "heterocyclyl" ring structures. Thus, when the '058 Patent

defines ring structures that can be directly bound at this position, *i.e.*, R^8 or R^9 itself, the definition affirmatively excludes a totally unsaturated ring (such as the present phenyl ring) at this position by explicitly specifying a "saturated cyclic group." On the other had, when the '058 Patent specifies cyclic groups that can be substituents on R^8 or R^9 when it is a C_{1-4}alkyl group, it recites the more inclusive ring designations of "carbocyclyl" and "heterocyclyl," which are defined at col. 4, lines 56-57, as including "saturated, partially saturated or unsaturated" ring structures.

In other words, the absence of a directly bound totally unsaturated phenyl ring structure from the definition of R^8 and R^9 in the '058 Patent is not simply by omission, but rather is by express exclusion through use of the designation "saturated cyclic group," instead of the more inclusive ring designations "carbocyclyl" or "heterocyclyl" which can only be indirectly bound at this position as a substituent on R^8 or R^9 when R^8 or R^9 is a C_{1-4}alkyl. The '058 Patent thus expressly and affirmatively teaches against making any substitution that would result in a compound having the directly bound totally unsaturated phenyl ring as required on the 8-position substituent of the present claims.

Withdrawal of this ground for rejection is therefore believed to be appropriate, and is respectfully requested.

Appln. No. 10/499,261

Claim 20 has been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 18 and 19 of copending Application No. 10/499,261. The Examiner asserts that "although the conflicting claims are not identical, they are not patentably distinct from each other because the complex composition of formula (I) which includes an additional active ingredient, i.e. PPAR alpha and/or gamma agonist." (Action paragraph 8 at pages 10-11).

This ground for rejection has been rendered moot by the above cancellation of claim 20, for reasons noted above and unrelated to this provisional rejection.

Appln. No. 10/499,379

Claim 20 has been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 18 and 19 of copending Application No. 10/499,379. The Examiner asserts that "although the conflicting claims are not identical, they are not patentably distinct from each other because the complex composition of formula (I) which includes an additional active ingredient, i.e. PPAR alpha and/or gamma agonist." (Action paragraph 9 at page 11).

First of all, the Examiner is advised that the cited application is not a "related application" of Applicants' assignee, does not relate to the subject matter of the present application, and apparently was cited in error. Application No. 10/499,379 published on December 16, 2004 as US 2004/0253689, and is directed to "Mutants of Human Insulin-Like Growth Factor Binding Protein-3 (IGFBP-3) And Uses Thereof."

In any event, regardless of what reference the Examiner may have intended to cite, this ground for rejection has been rendered moot by the above cancellation of claim 20, for reasons noted above and unrelated to this provisional rejection.

Appln. No. 10/502,355

Claims 12-21 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-20 of copending Application No. 10/502,355. The Examiner asserts that "although the conflicting claims are not identical, they are not patentably distinct from each other because the compositions and method of use of the compounds of formula (I) as well as the complex composition of formula (I) which includes an additional active ingredient, i.e. HMG Co-A reductase inhibitor, bile acid binder, etc." (Action paragraph 10 at page 11).

This ground for rejection remains provisional inasmuch as no claims have issued from or have been allowed in copending Application No. 10/502,355. Therefore, Applicants need not (and in fact are unable to) provide a substantive response at this time.

Appln. No. 10/520,939

Claims 10-21 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-32 of copending Application No. 10/520,939. The Examiner asserts that "although the conflicting claims are not identical, they are not patentably distinct from each other because the compositions and method of use of the compounds of formula (I) as well as the complex composition of formula (I) which includes an additional active ingredient, i.e. PPAR alpha and/or gamma agonist, HMG Co-A reductase inhibitor, bile acid binder, etc." (Action paragraph 11 at page 12).

This ground for rejection remains provisional inasmuch as no claims have issued from or have been allowed in copending Application No. 10/520,939. Therefore, Applicants need not (and in fact are unable to) provide a substantive response at this time.

Appln. No. 10/499,893

Claim 20 has been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 23 and 24 of copending Application No. 10/499,893. The Examiner asserts that "although the conflicting claims are not identical, they are not patentably distinct from each other because the complex composition of formula (I) which includes an additional active ingredient, i.e. PPAR alpha and/or gamma agonist." (Action paragraph 12 at page 12).

This ground for rejection has been rendered moot by the above cancellation of claim 20, for reasons noted above and unrelated to this provisional rejection.

Appln. No. 10/488,540

Claims 1-21 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-25 of copending Application No. 10/488,540. The Examiner asserts that "although the conflicting claims are not identical, they are not patentably distinct from each other because the compounds, compositions, process of preparing, complex compositions and method of use of the compounds of formula (I) are embraced by the compounds, compositions, process of

preparing, complex compositions and method of use of the compounds of formula (I) of 10/488,540 where R^1 and R^2 are both C_{1-6}alkyl." (Action paragraph 13 at pages 12-13).

This ground for rejection remains provisional inasmuch as no claims have issued from or have been allowed in copending Application No. 10/488,540. Therefore, Applicants need not (and in fact are unable to) provide a substantive response at this time.

Appln. No. 10/451,262

Claims 1-21 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-16, 20-69 and 73-76 of copending Application No. 10/451,262. The Examiner asserts that "although the conflicting claims are not identical, they are not patentably distinct from each other because the compounds, compositions, process of preparing, complex compositions and method of use of the compounds of formula (I) are embraced by the compounds, compositions, process of preparing, complex compositions and method of use of the compounds of formula (I) of 10/451,262 where R^3 and R^6 are both H; R^4 is MeS; R^5 is the compound of formula (IA) where D is O, R^7 is H; R^8 is H; A is hydrogen, hydroxyl or halo substituted phenyl; R^9 is H; m is 0; R^{11} is formula (IB) where R^{12} is H; p is 1; R^{13} is C_{1-4}alkyl; q is 0 or 1; X is -NHC(O)-; r is 0 or 1 and R^{15} is carboxy." (Action paragraph 14 at page 13).

This ground for rejection remains provisional inasmuch as no claims have issued from or have been allowed in copending Application No. 10/451,262. Therefore, Applicants need not (and in fact are unable to) provide a substantive response at this time.

Claim Objections

Claims 10-21 have been objected to under 37 CFR 1.75(c) as being in improper form because "a multiple dependent claim must be in the alternative." The undersigned is confused by the objection insofar as it has not also been applied to claims 4-6, which use the same "any one of claims x to y" format as objected-to claims 1-17 and 20, and insofar as it has been applied to claims 18 and 19, which are expressly in the alternative format of "according to claim x or claim y." The undersigned acknowledges that many of the original claims were improper multiple dependent claims, in that a multiple dependent claim cannot be dependent on another multiple dependent claim. However, the Examiner's basis for the present

objection, that "a multiple dependent claim must be in the alternative" seems irrelevant to what was, in fact, improper with some of the original claims.

In any event, it is believed that any proper basis for an objection to the original multiple dependent claims has been overcome by the above amendments canceling certain claims and making other claims dependent on claim 1 only. However, in view of the Examiner specific comment that "a multiple dependent claim must be in the alternative," the following observations are presented to make clear that the remaining multiple dependent claims are in an appropriate alternative form. Specifically, the term "any one of claims 1 or 4 to 8" used in amended claims 13 and 14 is most certainly in the alternative since it recites dependency on only one of claims 1, 4, 5, 6, 7 and 8 at a time. Moreover, this format of multiple dependency is expressly sanctioned by MPEP ¶ 608.01(n)I.A., which provides:

> ***A. Acceptable Multiple Dependent Claim Wording***
>
> Claim 5. A gadget according to claims 3 or 4, further comprising ---
>
> Claim 5. A gadget as in any one of the preceding claims, in which ---
>
> Claim 5. A gadget as in any one of claims 1, 2, and 3, in which ---
>
> Claim 3. A gadget as in either claim 1 or claim 2, further comprising ---
>
> Claim 4. A gadget as in claim 2 or 3, further comprising ---
>
> Claim 16. A gadget as in claims 1, 7, 12, or 15, further comprising ---
>
> Claim 5. A gadget as in any of the preceding claims, in which ---
>
> Claim 8. A gadget as in one of claims 4-7, in which ---
>
> Claim 5. A gadget as in any preceding claim, in which ---
>
> Claim 10. A gadget as in any of claims 1-3 or 7-9, in which ---
>
> Claim 11. A gadget as in any one of claims 1, 2, or 7-10 inclusive, in which ---

(MPEP ¶ 608.01(n)I.A., Rev. 3, August 2005; underlined emphasis added).

Any one of the underlined passages in the above quotation exemplifying "Acceptable Multiple Dependent Claim Wording" is the same as or equivalent to Applicants' recitation of "any one of claims 1 or 4 to 8," which clearly meets the basic requirement that a dependent claim can be dependent on only one preceding claim at a time. This may properly be accomplished by various wording, including the use of the alternative "or", but also by reciting "any one of", or "one of" etc. The multiple dependent wording of claims 13 and 14 is thus clearly acceptable, and it is respectfully requested that this objection be withdrawn.

Conclusion

It is believed that all grounds for rejection and/or objection have been addressed above and appropriately overcome by the above amendments and/or the foregoing remarks, or obviated by cancellation of the involved claims. Therefore, withdrawal of each ground for rejection and/or objection, and the allowance of all claims as amended above are respectfully requested.

EXCEPT for issue fees payable under 37 C.F.R. § 1.18, the Director is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a CONSTRUCTIVE PETITION FOR EXTENSION OF TIME in accordance with 37 C.F.R. § 1.136(a)(3).

Respectfully Submitted,
Morgan Lewis & Bockius LLP

Date: December 30, 2005 By: _____

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